EXHIBIT A

FDA Briefing Document

BLA 761176

Drug name: ^{131}I-omburtamab

Applicant: Y-mAbs Therapeutics, Incorporated

Oncologic Drugs Advisory Committee Meeting

October 28, 2022

Division of Oncology 2/Office of Oncologic Diseases

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the assessment of the evidence of effectiveness for ^{131}I-omburtamab to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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GLOSSARY

Include any acronyms or abbreviations used four or more times in the AC BD. Each instance of terms appearing three or fewer times should be spelled out rather than abbreviated.

Acronyms and abbreviations should be spelled out at first use in the Executive Summary, main body (if not spelled out in the Executive Summary), and Appendix (if not spelled out in the Executive Summary or main body). The sample list below includes commonly used acronyms and may be used as a starting point.

AC	Advisory Committee
BD	Briefing Document
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CGCCR	Central German Childhood Cancer Registry
CI	Confidence Interval
CNS	Central Nervous System
CSI	Craniospinal irradiation
DOR	Duration of Response
FDA	Food and Drug Administration
IA	integrated assessment
LM	Leptomeningeal
MSKCC	Memorial Sloan Kettering Cancer Center
ODAC	Oncologic Drugs Advisory Committee
ORR	Overall Response Rate
OS	Overall Survival
RANO	Response Assessment in Neuro-Oncology
REMS	Risk evaluation and mitigation strategy
RPM	Regulatory Project Manager
SAP	Statistical Analysis Plan
SD	standard deviation

1 EXECUTIVE SUMMARY/DRAFT POINTS FOR CONSIDERATION BY THE ADVISORY COMMITTEE

On March 31, 2022, Y-mAbs Therapeutics, Incorporated (Y-mAbs) submitted a Biologics License Application (BLA) for ^{131}I-omburtamab. The Applicant is seeking traditional approval for the following indication:

- For the treatment of central nervous system/leptomeningeal (CNS/LM) metastases in pediatric patients with neuroblastoma following standard multimodality treatment for CNS disease.

^{131}I-omburtamab is an iodine-131 radiolabeled murine monoclonal antibody that binds to the B7-H3 (also known as cluster of differentiation 276, CD276) antigen, which is expressed on the surface of neuroblastoma tumor cells (Castriconi R 2004). ^{131}I-omburtamab is administered as an intraventricular infusion using an intracerebroventricular access device (e.g., an Ommaya reservoir). The proposed dosage is based on patient age and consists of a total of two doses given four weeks apart.

The U.S. Food and Drug Administration (FDA) is convening the Oncologic Drugs Advisory Committee (ODAC) to discuss concerns relating to the totality of evidence provided by the Applicant to support that intraventricular administration of ^{131}I-omburtamab following receipt of a multimodality treatment regimen improves overall survival (OS) in pediatric patients with neuroblastoma with CNS/LM metastases.

The primary efficacy data supporting this application are derived from a single-center investigator-initiated single-arm trial, Study 03-133, entitled “Phase I Study of Intrathecal Radioimmunotherapy using ^{131}I-omburtamab for Central Nervous System/Leptomeningeal Neoplasms”. The trial was conducted at Memorial Sloan Kettering Cancer Center (MSKCC) and included pediatric patients with neuroblastoma that relapsed in the central nervous system (CNS) or leptomeninges (CNS/LM). Patients with rapidly worsening neurological status and obstructive or symptomatic communicating hydrocephalus were ineligible.

The efficacy population consists of a subset of 94 pediatric patients ages 0.9 to 13 years with CNS/LM relapsed neuroblastoma who received ^{131}I-omburtamab as an intracerebroventricular infusion at a dose of 25 mCi, 33.5 mCi, or 50 mCi based on age. Patients received up to 2 doses spaced 5 weeks apart, with the second dose at the discretion of the treating physician in the absence of disease progression or unacceptable toxicity. The first patient was enrolled in 2004, and the last patient enrolled in 2018. The primary endpoint in Study 03-133 was overall survival (OS) at 3 years. OS was calculated from the date of first diagnosis of CNS/LM relapse until death or the latest date the patient was confirmed to be alive. Tumor responses were not systematically analyzed in this study. After CNS/LM relapse and prior to receiving ^{131}I-omburtamab, all patients received at least one type of CNS-directed therapy (surgery, chemotherapy, and/or radiotherapy) and the majority of patients (76%) received all three treatment modalities. The 3-year OS rate after CNS/LM relapse in the efficacy population of 94 patients was 54% (95% Confidence Interval [CI]: 0.43, 0.64).

The OS results in Study 03-133 were compared with an external control constructed from data from the Central German Childhood Cancer Registry (CGCCR), which includes clinical data from patients with Stage 4 neuroblastoma included in the German national neuroblastoma clinical trials NB90, NB97 and NB2004 from 1990 to 2015. The Applicant identified 79 patients in the source population who received at least one type of post-CNS relapse treatment (radiotherapy, chemotherapy, or surgery).

The application also included interim data from an ongoing international multi-center single-arm trial, Study 101, which investigates the safety and efficacy of ^{131}I-omburtamab in pediatric patients with neuroblastoma with relapse in the CNS including parenchymal or LM metastases. Patients with rapidly worsening neurological status and obstructive or symptomatic communicating hydrocephalus are ineligible. The primary endpoint of the trial is 3-year OS rate, with a key secondary endpoint of overall response rate (ORR) based on Response Assessment in Neuro-Oncology (RANO) criteria for brain metastases or European Association of Neuro-Oncology-European Society for Medical Oncology (EANO-ESMO) criteria for leptomeningeal metastases according to blinded independent central review (BICR). Study 101 is fully enrolled, but survival data remain immature.

The safety population consists of pediatric patients with neuroblastoma with CNS/LM metastases who received the proposed recommended dose in Study 03-133 (n=94) and Study 101 (n=32). The key safety concerns regarding treatment with ^{131}I-omburtamab include risk associated with intraventricular delivery (e.g., risks due to placement of an Ommaya-like reservoir, infusion-related reactions, neurotoxicity and chemical meningitis) and risk of off-target effects due to exposure to radioactive iodine outside of the subarachnoid space (e.g., myelosuppression and secondary malignancy). The most common serious adverse reactions (>10% of patients) were related to myelosuppression. Permanent discontinuation of ^{131}I-omburtamab due to an adverse reaction occurred in 19% of patients in Study 03-133 and 28% of patients in Study 101 and were primarily related to myelosuppression with the exception of chemical meningitis in 3% of patients (3 cases in Study 03-133 and 1 case in Study 101). One case of fatal intracranial hemorrhage occurred in a patient with Grade 4 thrombocytopenia in Study 101.

To receive FDA approval, a drug or biologic product must demonstrate substantial evidence of effectiveness through adequate and well-controlled studies (21 CFR 314.126). To establish effectiveness, it is essential to distinguish the effect of the drug "from influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation" (21 CFR 314.126[a]).

Efficacy results submitted by the Applicant rely on an assessment of OS in a single-arm trial (Study 03-133). As discussed in the FDA guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018), OS should generally be evaluated in randomized trials because data from externally controlled trials may not be reliable or interpretable. Apparent differences in outcome between external controls and current treatment groups can arise from factors other than the drug under investigation, such as differences in patient or disease characteristics, supportive care, concomitant treatments, or other factors. Randomized studies minimize the effect of both known and unknown differences between populations by providing a direct outcome comparison. Despite the significant limitations associated with interpretation of OS in non-randomized settings, there may be contexts where a randomized trial is difficult to conduct. For serious rare diseases with unmet medical

need, there is interest regarding use of an external control in which all enrolled patients receive the investigational drug without randomization to a concurrent comparator group.

Because random assignment is not a feature of external control designs, there may be known or unknown differences in important prognostic covariates such as concomitant treatments that lead to differences in outcome that are unrelated to the investigational treatment. In addition to the lack of ability to eliminate systematic differences between nonconcurrent groups, the lack of blinding can introduce bias into treatment decisions and assessment of outcomes in the investigational arm [FDA guidance for industry, *Rare Diseases: Common Issues in Drug Development* (2019)].

The inability to eliminate systematic differences between nonconcurrent treatment groups is a major limitation of externally controlled designs. This limitation generally restricts use of external control designs to assessment of serious disease when a randomized trial is not feasible or ethical, and when certain conditions are present. In circumstances where randomization is not felt to be feasible, efficacy in oncology single-arm trials has relied on objective tumor response which removes the uncertainty around attribution of the effect to the drug under study rather than other confounding influences.

As described in FDA draft guidances for industry [*Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* (2019) and *Rare Diseases: Common Issues in Drug Development* (2019)], the following characteristics can strengthen the level of support for effectiveness provided by an externally controlled trial:

- the natural history of a disease is well defined (i.e., has a highly predictable disease course that can be objectively measured and verified),
- the external control population is very similar to that of the treatment group,
- concomitant treatments that affect the primary endpoint are not substantially different between the external control population and the trial population, and
- the results provide compelling evidence of a change in the established progression of disease (such as partial or complete response in a disease where spontaneous regression is not observed).

As described in detail in subsequent sections of this document, these characteristics only partially apply at best to the externally controlled comparison of overall survival in this application for the following reasons:

- Although patients with CNS/LM relapsed neuroblastoma have a high unmet medical need and a generally poor prognosis, there is evidence to suggest heterogeneity in patient outcome and available information indicates that survival has improved over time (see Section 2.1 and Table 14).
- Although the patient populations are comparable with respect to certain prognostic baseline demographic and disease-related characteristics (see Table 8), there are potentially important population differences because patients enrolled in Study 03-133 had to have sufficiently

recovered from prior CNS-directed treatment to travel to the MSKCC site and receive ^{131}I-omburtamab. Additionally, there are potential differences in clinical care between the United States and Germany.

- There are substantive differences in concomitant anticancer treatments that appear to impact survival (see Table 11 and Table 12).
- Although the Applicant states that when administered into the intraventricular space, ^{131}I-omburtamab targets B7-H3-expressing tumor cells in the entire CSF compartment, including micro-metastatic CNS disease, the application does not contain reliable response data to support the antitumor effect of ^{131}I-omburtamab when administered to patients following receipt of prior CNS-directed treatment, or that micrometastatic disease is consistently present in the CSF in patients enrolled in these trials (see discussion of Issue #3 in Section 3.1.3).

FDA has identified three key review issues regarding data submitted to provide substantial evidence of effectiveness for this application.

- **The external control population is not fit-for-purpose as a comparator due to substantive differences between the study and control populations that limit the ability to attribute survival differences to the effect of ^{131}I-omburtamab.**
  - In particular, patients in Study 03-133 received multimodality treatment for CNS/LM relapse prior to ^{131}I-omburtamab that was generally more intensive than treatment documented in the external control population. There is a clear trend toward improved survival with higher treatment intensity in the external control population. For the 79 patients who received at least one treatment modality for CNS/LM relapse in the CGCCR external control, the 3-year OS rate from the time of CNS relapse was 15% (95% CI: 0.08, 0.24). In the subset of patients who received radiation, surgery, and chemotherapy (n=21), the 3-year OS rate was 38% (95% CI: 0.18, 0.58).
  - The external control data are not contemporaneous with the dates of enrollment in Study 03-133 and available data indicate that OS in patients with CNS/LM neuroblastoma has improved over time.
  - There are other potential sources of bias due to population selection and differences in treatment patterns between countries and over time.

- **Recognizing the level of evidence provided and need for regulatory flexibility, FDA performed additional analyses to examine bias and results reinforce that differences in survival cannot be reliably attributed to ^{131}I-omburtamab.**

  - After adjusting for the number of post-CNS/LM relapse CNS-directed therapy modalities, choice of index date, and the era of therapy, the apparent differences in survival between the Study 03-133 and external control populations shrink substantially in contrast to comparisons that do not adjust for these factors (median OS 31.3 months [95% CI: 20.2, 57.6] in Study 03-133 vs 24.4 months [95% CI: 6.0, NE] in the external control; hazard ratio (HR): 1.02 [95% CI: 0.48, 2.16]) (see Table 16 and Figure 5).

- Statistical methodology is limited by small sample sizes and can only partially adjust for some known sources of bias and cannot adjust for unknown sources of bias.

- **The application does not include reliable response rate data to provide supportive evidence of the treatment effect of ^{131}I-omburtamab. No patient in Study 101 demonstrated a response that can be unequivocally attributed to ^{131}I-omburtamab.**
  - ORR data was not collected in Study 03-133.
  - There are limited ORR data from Study 101 with substantial uncertainty regarding attribution of the response to ^{131}I-omburtamab, the accuracy of the response determinations themselves, or both.
    - Among the 20 patients with imaging evidence of CNS/LM disease, the Applicant reports 7 responders according BICR; however, responses were not confirmed by subsequent imaging following documentation of initial response in 3 of these patients.
    - Missing data make assessment of LM disease uninterpretable. EANO-ESMO guidelines incorporate clinical status, cytology and imaging (as defined as improved, stable, or worse) to define a response. Among the 2 patients classified as responders with LM disease, all had negative cytology at baseline and there is insufficient information in most cases to confirm baseline disease status and assess response.
    - Adjudication was required by a third reviewer in all cases due to disagreement between the two blinded independent reviewers (see Appendix), underscoring the challenge in assessing imaging for patients with CNS/LM relapsed neuroblastoma in Study 101.
    - Assessment of the contribution of effect of ^{131}I-omburtamab was limited by clinical factors such as receipt of chemotherapy between the initial and confirmatory scans documenting response and receipt of radiation and/or chemotherapy within 3-4 weeks of the baseline imaging prior to ^{131}I-omburtamab.

When considered together, the complex review issues described above result in a large degree of uncertainty regarding whether the observed differences in overall survival between the single-arm Study 03-133 and external control populations are due to ^{131}I-omburtamab or whether they are due to differences in other anticancer treatments, supportive care regimens, unknown differences between the two populations, or a combination of these factors.

In summary, the identified substantive review issues call into serious question whether the CGCCR-derived patient population is an appropriate comparator. In addition, there is no reliable information on tumor response rate, leading to significant questions as to whether the submitted study can be considered an adequate and well-controlled trial necessary to establish effectiveness. Without substantial evidence of effectiveness, FDA cannot determine whether the risk:benefit relationship for use of ^{131}I-omburtamab in patients with CNS/LM relapsed neuroblastoma is favorable.

1.1 Purpose/Objective of the AC Meeting

The FDA Division of Oncology 2 is convening this ODAC meeting to discuss the following key issues, which the FDA considers relevant to a determination regarding whether substantial evidence of

effectiveness has been established for ^{131}I-omburtamab in pediatric patients with neuroblastoma with CNS/LM metastases.

1. The external control population is not fit-for-purpose as a comparator due to substantive differences between the study and control populations that limit the ability to attribute survival differences to the effect of ^{131}I-omburtamab.
2. Recognizing the level of evidence provided and need for regulatory flexibility, FDA performed additional analyses to examine bias and results reinforce that differences in survival cannot be reliably attributed to ^{131}I-omburtamab.
3. The application does not include reliable response rate data to provide supportive evidence of the treatment effect of ^{131}I-omburtamab.

Given the magnitude of these uncertainties and limitations, FDA requests discussion regarding the assessment of efficacy in this application.

1.2 Context for Issues to Be Discussed at the AC

Disease Background

Neuroblastoma is a childhood cancer that originates in the sympathetic nervous system, typically occurring in or near the adrenal glands. It accounts for 7-10% of childhood cancers, with more than 650 cases diagnosed per year in the US (PDQ Neuroblastoma Treatment). Approximately half of these patients have high-risk neuroblastoma (DuBois 2022); approximately 6% of patients with high-risk neuroblastoma who experience metastatic relapse have metastases to the CNS or LM (Berlanga, 2021).

Median survival with CNS/LM relapse has historically been reported to be less than one year (PDQ Neuroblastoma Treatment; Berlanga, 2021; Kramer 2001, Matthay, 2003); however, there is some literature to suggest that survival has improved over time and long-term remission has been reported in patients who received craniospinal irradiation and chemotherapy (Kellie 1991; Berlanga 2021). Moreover, the external control data provided by the Applicant also indicate that survival has improved over the past 2 decades (see Section 3.1.3, Issue #2, below).

There are currently no FDA-approved therapies for neuroblastoma with CNS/LM relapse and standard of care is not well defined. A typical treatment approach in the US includes radiation therapy, specifically craniospinal irradiation, which has only been described in retrospective, single-arm studies (Kellie 1991, Luo 2020). Higher than previously reported survival in these single-arm cohorts has been thought to be due in part to selection bias, as patients receiving multimodal treatment are likely to have better prognosis (Berlanga 2021). Chemotherapy with CNS-penetrant agents such as irinotecan and temozolomide has also been suggested for use in this population, however well-controlled trials studying their utility have not been performed (Kushner 2006).

Drug Product Information

^{131}I-omburtamab is a radiolabeled murine monoclonal antibody that targets B7-H3, which is known to be overexpressed on the surface of human neuroblastoma tumor cells. ^{131}I-omburtamab is delivered via intracerebroventricular infusion using an Ommaya reservoir or programmable cerebrospinal fluid (CSF) shunt (e.g., ventriculoperitoneal shunt). Although intracerebroventricular infusion is a validated method of drug delivery for cancers that metastasize to the leptomeninges, the intraparenchymal exposure of drugs delivered via CSF is considered minimal (Ratcheson R 1968, Blasberg RG 1975). To date, the Applicant has not provided preclinical or radioisotope imaging evidence of CNS parenchymal penetration for ^{131}I-omburtamab via intracerebroventricular delivery.

Regulatory Considerations

FDA approval requires substantial evidence of effectiveness to be established by two or more adequate and well-controlled trials or by a single adequate and well-controlled trial with supportive evidence (FDA draft guidance for industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* 2019*)*. The quality of clinical evidence to establish effectiveness and the resulting level of certainty about the demonstration of substantial evidence is impacted by the selection of trial design and endpoints, as well as statistical considerations. The "substantial evidence" of effectiveness standard in the statute refers to both the quality and quantity of evidence. In 1962, Congress defined substantial evidence as "evidence consisting of adequate and well-controlled investigations…on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have…" (FD&C Act section 505(d) [21 U.S.C. § 355(d)]). Although this definition applied to drugs, FDA has also generally considered "substantial evidence" of effectiveness to be necessary to support licensure of a biological product under section 351 of the PHS Act.

In oncology, overall survival is typically considered the gold standard efficacy endpoint to support traditional approval since prolongation of survival is a direct clinical benefit and also reflects drug safety. For regulatory purposes, randomized trials are needed with rare exception to assess the effect of a drug on overall survival because randomization controls for both known and unknown prognostic factors. In specific circumstances, such as when randomized trials are infeasible or impractical, an adequate and well-controlled trial may rely on an external control; however regulations stipulate that the comparison of the results of treatment occur in "comparable patients or populations" (21 CFR 314.126).

As discussed in the 2019 FDA draft guidance for industry*, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, externally controlled trials differ in several important ways from randomized trials. Most notably, randomization is not a feature of external control designs. As a result, there may be differences in baseline patient characteristics or concomitant treatments in the trial population compared to the external control population that lead to differences in outcomes that are unrelated to the investigational treatment.

The draft guidance indicates that the level of support for effectiveness provided by an externally controlled trial is strengthened if the following conditions are present:

- the natural history of a disease is well defined,

- the external control population is very similar to that of the treatment group,
- concomitant treatments that affect the primary endpoint are not substantially different between the external control population and the trial population, and
- the results provide compelling evidence of a change in the established progression of disease (such as partial or complete response in a disease where spontaneous regression is not observed).

As discussed in the Executive Summary above, the externally controlled comparison only partially meets aspects of the first two conditions and the latter two are not present.

When considering this Application, the FDA recognizes that it is appropriate to exert broad regulatory flexibility in applying the statutory standards of safety and effectiveness in the evaluation of new therapies intended to treat persons with life-threatening illnesses, particularly when there is no satisfactory alternative therapy, as outlined in 21 CFR 312, subpart E (21 CFR 312.8). The FDA also accepts that a higher degree of uncertainty may be acceptable given the poor prognosis of pediatric patients with neuroblastoma with CNS/LM metastases. Nevertheless, the types of regulatory flexibility that are appropriate may depend on scientific factors in addition to the degree of unmet medical need. In order to render an approval decision, FDA must reach the conclusion that the application contains substantial evidence of effectiveness, taking into account the level of uncertainty and degree of regulatory flexibility that are appropriate in the context of the strength of the scientific evidence in addition to risks of the drug and degree of unmet medical need. The requirement for substantial evidence of effectiveness generated by an adequate and well controlled trial with supportive evidence or two or more adequate and well-controlled trials applies irrespective of the degree of unmet medical need.

1.3 Brief Description of Issues for Discussion at the AC

FDA approval requires substantial evidence of effectiveness to be established (FD&C Act section 505(d) [21 U.S.C. § 355(d)]); such evidence must be generated by one or more adequate and well-controlled investigations. To establish a drug's effectiveness, it is essential to distinguish the effect of the drug "from other influences, such as spontaneous change in the course of the disease, placebo effect, *or biased observation* (emphasis added)" (21 CFR 314.126).

The Division of Oncology 2 sought an ODAC meeting to facilitate discussion regarding the BLA for ^{131}I-omburtamab, which was submitted based on results of a single-arm, single-center trial with an overall survival endpoint, employing an external control arm proposed to interpret the overall survival results.

1. **<u>The external control population is not fit-for-purpose as a comparator due to substantive differences between the study and control populations that limit the ability to attribute survival differences to the effect of omburtamab.</u>**
    - **Differences in treatment intensity:** The approach to treatment of CNS relapse treatment differed between the Study 03-133 and external control populations, with patients in Study 03-133 generally receiving more intensive treatment (Table 1).

Table 1: Differences in therapies received for CNS/LM relapse in Study 03-133 and CGCCR

	Study 03-133 (prior to receiving ^{131}I-omburtamab) N=94	External control* N=79
Treatment Modality	**n (%)**	**n (%)**
Radiation Therapy	87 (93%)	40 (51%)
Craniospinal Irradiation	86 (91%) 18 or 21 Gy +/- boost	0 patients
Chemotherapy	92 (98%) *Typically included temozolomide and irinotecan.*	67 (85%) *Few patients received temozolomide (6%) or irinotecan (5%). Typically included topotecan and etoposide.*
Received all treatment modalities (radiation therapy, chemotherapy and surgery)	**71 (76%)**	**21 (27%)**

*based on the subset of patients who received at least one type of treatment for CNS/LM disease

- **Post ^{131}I-omburtamab therapies not captured:** The gap in treatment intensity is likely to be wider than what is reflected in Study 03-133 data because post-^{131}I-omburtamab treatment was not systematically captured in this study. Based on typical US treatment practices, it is likely that many patients in Study 03-133 received additional therapy following ^{131}I-omburtamab which could contribute to longer survival. Interim data from the supportive study (Study 101) indicate that 34 of 50 (68%) of patients received anti-cancer therapy (chemotherapy, immunotherapy, radiotherapy, surgery, or a combination of both) after ^{131}I-omburtamab.

- **Baseline clinical status likely better in Study 03-133**: In order to qualify for enrollment in Study 03-133 and receive ^{131}I-omburtamab, patients had to be well enough to travel to the single site (MSKCC) and sufficiently recover from intensive multimodality treatment; this differs from the selection criteria for the external control and represents a major confounding factor.

- **Potential for additional unknown clinically relevant differences :** There may be additional differences between the populations that have not been identified due to incomplete data capture for key post-CNS relapse treatment variables (such as dose of chemotherapy and radiation) and unknown differences in clinical care between the United States and Germany.

In summary, FDA cannot reliably attribute the observed OS difference to ^{131}I-*omburtumab.* There are multiple clinically important known differences between the Study 03-133 and external control populations including differences in treatment intensity, with these differences insufficiently characterized due to lack of capture of information about post-^{131}I-omburtamab therapies in Study 03-133, and patient selection differences that may result in enrollment of patients with better clinical status at baseline in Study 03-133. Additionally it is likely that there are other unknown clinically relevant differences. Taken together, there is a large degree of uncertainty regarding whether differences in survival between these populations are due to ^{131}I-omburtamab or whether they are due to differences in other anticancer treatment, supportive care regimens, unknown differences between the two populations, or a combination of these factors.

2. **Recognizing the level of evidence provided and need for regulatory flexibility, FDA performed additional analyses to examine bias and results reinforce that differences in survival cannot be reliably attributed to ^{131}I-omburtamab.**

   Sources of bias and the statistical approach to adjust for some of these biases are described below.

   - **Population Selection:** As described in Review Issue #1 above, patients enrolled in Study 03-133 (n=94) generally received more intensive treatment compared to patients in the CGCCR dataset (n=79; see Table 1), both in terms of number and types of post-CNS relapse treatments.

     The Applicant proposed to provide efficacy analyses using the following modality groupings to identify an external control subpopulation that was more comparable to the Study 03-133 patient population:

     - Modality Group 1: patients who received at least one post-relapse therapy (surgery, radiation, or chemotherapy)
       - Includes all patients in Study 03-133 (n=94) and represents the subset of the CGCCR population used for the external control (n=79).
       - From time of CNS relapse, the **median OS of this subgroup in the external control was 9.9 months (95% CI: 6.9, 14.0)**.
     - Modality Group 2: patients who received post-relapse radiation therapy and at least one other treatment modality (surgery or chemotherapy)
       - Includes 91% (n=86) of patients in Study 03-133 and 44% (n=35) of patients in the external control population.
       - From time of CNS relapse, the **median OS of this subgroup in the external control was 16.0 months (95% CI: 10.0, 29.8)**.

- Modality Group 3: patients who received post-relapse radiation therapy, surgery, and chemotherapy
  - Includes 76% (n=71) of patients in Study 03-133 and 27% (n=21) of patients in the external control population.
  - From time of CNS relapse, the **median OS of this subgroup in the external control was 29.8 months (95% CI: 11.7, NE)**.

These analyses shows a clear trend for improved survival in patients in the external control population who received CNS-directed therapy that was more comparable to treatment received by Study 03-133 patients; this highlights the magnitude of uncertainty associated with attribution of survival differences to ^{131}I-omburtamab based on OS comparisons between the Study 03-133 and external control populations.

- **Immortal time (credited survival):** The Applicant proposed to use the start date for the last modality type of post-CNS relapse treatment (Index Date A) as the index date for survival analyses. In Study 03-133, this represents the start of the last type of post-CNS relapse treatment received prior to ^{131}I-omburtamab. In order to be included in the study population for Study 03-133, patients must have survived from the period of time between the start of the last type of post-CNS relapse treatment (Index Date A) to the time of initial receipt of ^{131}I-omburtamab (Index Date D); this time period is considered "immortal time" during which patients in Study 03-133 could not have died. This biases any analysis of survival time in favor of the trial population because patients were not required to have survived following post-CNS relapse treatment to be included in the external control population.
  - In Study 03-133, the median time between Index Date A and Index Date D (Immortal Time) was 3.1 months (range 0.6 to 30 months). See Figure 3.
  - Among the 79 patients who received any post-CNS relapse chemotherapy, radiation therapy, or surgery in the external control, 24 patients (30%) died within 3.1 months of Index Date A. This subset of patients would not have lived long enough to receive treatment with ^{131}I-omburtamab if they had otherwise been eligible to enroll in Study 03-133, reflecting immortal time bias.

- **Study time period differences:** In order to maximize the sample size for the propensity score analysis of overall survival, FDA encouraged the Applicant to capture external control data from patients enrolled in the CGCCR from 1990 to 2015 (patients diagnosed with CNS/LM relapse between 1991 and 2020), whereas Study 03-133 included patients diagnosed with CNS/LM relapse between 2005 and 2018. Differences in treatment era and changing cancer-directed or supportive care over time may result in improved survival over time which disproportionately impacts OS comparisons with the external control arm.

Analysis of the data submitted to the Application show that the subpopulation of patients in the external control who received at least one type of therapy for CNS relapse during the period of time contemporaneous with Study 03-133 (September 21, 2005 and later) had longer overall survival.

- 1990-2005
  - Included no patients in Study 03-133 and 44 patients (56%) in the external control who received at least one post-CNS relapse treatment
  - From time of CNS relapse, **median OS in the external control: 9.6 months (95% CI: 5.6, 11.7)**
- 2005-2020 (contemporaneous timeframe)
  - Included all patients in Study 03-133 (2005-2018)
  - Included 35 patients (44%) in the external control who received at least one post-CNS relapse treatment, 2005-2020)
  - From time of CNS relapse, **median OS in the external control: 15.7 months (95% CI: 5.3, 29.8)**

- **FDA's approach to addressing these sources of bias:** FDA analyses included propensity score-based weighting in the primary analysis and adjusting for major sources of bias through conduct of sensitivity analyses. In FDA's most conservative sensitivity analysis, the populations of Study 03-133 and the external control were restricted to patients in Modality Group 2 with first CNS relapse occurring on September 21, 2005 or later, representing a more contemporaneous population. FDA then used Index Date D in the Trial population and Index Date A in the external control population (Index Dates A/D) to illustrate and adjust for the effect of observed immortal time bias.
  - This results in a comparison of 77 patients in Study 03-133 to 17 patients in the external control (weighted to 19.3 patients).
  - Median survival in the study and external control is 31.3 vs. 24.4 months, respectively (hazard ratio 1.02, 95% CI: 0.48, 2.16).
  - The small sample size in the control arm (n=17) limits statistical inference and interpretation.

- **Statistical analyses cannot adjust for all sources of bias:** There are other important potential sources of bias that cannot be quantified, such as differences in supportive care between Germany and the US, differences in types of radiation received, post-^{131}I-omburtamab treatment received by patients in Study 03-133, and other biases inherent in a single-center study.

3. **The application does not include reliable response rate data to provide supportive evidence of the treatment effect of ^{131}I-omburtamab. No patient in Study 101 demonstrated a response that can be unequivocally attributed to ^{131}I-omburtamab.**

- There are limited ORR data from Study 101 with substantial uncertainty regarding attribution of the response to ^{131}I-omburtamab, the accuracy of the response determinations themselves, or both.
  - Among the 20 patients with imaging evidence of CNS/LM disease, the Applicant reports 7 responders according BICR; however, for 3 patients (one with parenchymal disease only and two with parenchymal and LM disease), responses were not confirmed. FDA considers durability of response a critical component of response assessment and confirmation of response on follow-up imaging provides assurance regarding consistency of interpretation of response (which is particularly important when responses are difficult to assess, such as with LM metastases) and an assessment of the clinical importance of the response since transient responses are not likely to be meaningful.
    - RANO group criteria for brain metastasis were used to assess parenchymal disease and require confirmation of response after at least 4 weeks; 3 of the 5 reported responders with parenchymal disease did not have confirmed responses.
    - EANO-ESMO guidelines incorporate clinical status, cytology and imaging (defined as improved, stable, or worse) to define a response. All patients with LM disease were cytology negative, lacking confirmation of baseline disease. For patients with LM, there is insufficient information in most cases to assess response.
  - LM disease and treated parenchymal disease can be challenging to interpret as evidenced by adjudication required for most patients. For all reported responders, adjudication was required by a third reviewer due to disagreement between the two blinded independent reviewers (see Appendix); in many cases where one reviewer assessed the imaging as LM disease or a response, the other reviewer assessed the imaging as no evidence of disease.
  - Assessment of the contribution of effect of ^{131}I-omburtamab was limited by clinical factors such as receipt of chemotherapy between the initial and confirmatory scans documenting response and receipt of radiation and/or chemotherapy within 3-4 weeks of the baseline imaging prior to ^{131}I-omburtamab (see Appendix Table).
  - These observations introduce substantial uncertainty regarding attribution of the response to ^{131}I-omburtamab, the accuracy of the response determinations themselves, or both.

1.4 Draft Points for Consideration

- Discuss if real-world data (RWD) from the Central German Childhood Cancer Registry are appropriate for comparison of overall survival with Study 03-133, taking into account the known differences in the study populations and other potential sources of bias.
- Discuss whether additional information is needed to assess the benefit of ^{131}I-omburtamab for neuroblastoma with CNS/LM relapse.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Neuroblastoma is a childhood cancer of neural crest origin that accounts for 7-10% of childhood cancers with more than 650 cases diagnosed per year in the US (PDQ Neuroblastoma Treatment). Approximately half of these patients have high-risk neuroblastoma (DuBois 2022) and approximately 6% of patients with high-risk neuroblastoma who experience metastatic relapse have metastases to the CNS or LM (Berlanga, 2021).

Median survival with CNS/LM relapse has historically been reported to be less than one year (PDQ Neuroblastoma Treatment; Berlanga, 2021; Kramer 2001, Matthay, 2003); however, long-term survivors have been reported. In the largest prospective natural history study of pediatric patients with neuroblastoma with CNS relapse (n=53), the European Society of Paediatric Oncology Neuroblastoma Group reported a 3-year survival of 8% (Berlanga 2021); however, 18 patients (34%) received no treatment for CNS relapse, while 19 patients (36%) received at least 2 modalities of treatment (e.g., surgery and chemotherapy), highlighting the diversity of treatments received by these patients. Of the 53 patients, 13 (25%) lived longer than 15 months, and 7 (13%) lived longer than two years, including 3 (5%) who were still alive at the time of publication (120+ months, 59+ months and 56+ months).

There are currently no FDA-approved therapies for neuroblastoma with CNS relapse and no Class I, Class II, or Class III evidence exists to support a standard of care. Available therapies include radiation therapy, which has included both focal and craniospinal irradiation (Croog 2010, Kellie 1991, Luo 2020, Rowland 2012). Single-center retrospective studies have identified long-term responders among patients who received craniospinal irradiation in particular (Croog 2010, Kellie 1991). Notably, some of the patients receiving craniospinal irradiation in some of these studies (Croog 2010) also received ^{131}I-omburtamab. Other authors have suggested that these results may be related in part due to selection bias, as patients fit enough to receive multi-modality therapy may have a better prognosis (Berlanga 2021).

Chemotherapy with CNS-penetrant agents such as irinotecan and temozolomide has also been suggested for high-risk neuroblastoma (Kushner 2006). Irinotecan and temozolomide have been used as a backbone chemotherapy for recent trials of additional agents for relapsed or refractory neuroblastoma (Mody 2017, Mody 2020). The outcomes of irinotecan and temozolomide for neuroblastoma with CNS relapse have not been well described.

2.2 Pertinent Drug Development and Regulatory History

^{131}I-omburtamab is an iodine-131 radiolabeled murine monoclonal antibody that binds to the B7-H3 (also known as cluster of differentiation 276, CD276) antigen, which is expressed on the surface of neuroblastoma tumor cells. ^{131}I-omburtamab is administered as an intraventricular infusion using an intracerebroventricular access device (e.g., an Ommaya reservoir). The proposed dosage is based on patient age and consists of a total of two doses given four weeks apart.

Development of ^{131}I-omburtamab was initiated by MSKCC with Protocol 03-133, submitted on January 16, 2004 to IND 009351. The FDA granted Rare Pediatric Disease (RPD) Designation and Orphan Drug Designation (ODD) for the treatment of neuroblastoma on July 20, 2016 and August 29, 2016, respectively. On May 18, 2017, FDA granted Breakthrough Therapy Designation (BTD) to ^{131}I-omburtamab for the treatment of relapsed neuroblastoma with CNS/LM metastases based on survival data from Study 03-133 compared to a literature-based external control. On October 1, 2017, ownership of the IND was transferred from MSKCC to Y-mAbs.

The FDA held multiple meetings with Y-mAbs to facilitate the clinical development of ^{131}I-omburtamab (Table 2). On August 5, 2020, Y-mAbs completed submission of the original BLA. On October 2, 2022, FDA issued a Refuse to File (RTF) letter for both clinical and CMC-related issues (Table 3).

As summarized in Table 3, FDA met with Y-mAbs multiple times to discuss the issues outlined in the RTF letter and to reach agreement on how to address each issue. FDA repeatedly expressed concerns that the CGCCR external control data may not be fit-for-purpose as a direct comparator for the overall survival data from patients in Study 03-133 because the patient populations may not have sufficient comparability for a valid comparison. FDA also repeatedly noted that direct evidence of the anti-tumor effect of ^{131}I-omburtamab through assessment of overall response rate and duration of response as determined by a blinded independent radiology committee is needed to provide supportive evidence of the effectiveness of ^{131}I-omburtamab.

On March 31, 2022, Y-mAbs elected to resubmit the BLA prior to reaching agreement with the FDA on the content of the application.

Table 2: Regulatory Interactions Prior to Initial BLA Submission

Date	Key Interactions
7/16/2004	Protocol 03-133 was submitted to IND 009351.
5/18/2017	BTD granted for the treatment of pediatric patients with relapsed or refractory neuroblastoma who have CNS/LM metastases based on survival data from 03-133 compared to literature-based description of the natural history of disease. • FDA stated these data provided preliminary clinical evidence that ^{131}I-omburtamab may demonstrate substantial improvement in overall survival; however, the data did not constitute substantial evidence of the safety and effectiveness required to support an approval. At a prior meeting (12/9/2016), FDA stated that **additional data, including evidence of durable objective response, are necessary to provide the level of evidence needed to support an approval**. • FDA also noted that there were **important limitations to the data from Study 03-133** such as the **ability to isolate the treatment effect** of ^{131}I-omburtamab from other treatments for relapsed disease and that a multicenter clinical trial is needed to demonstrate that results obtained by MSKCC could be reproduced by other sites.
6/14/2017	Pre-IND meeting to discuss the design of Study 101, a multicenter trial intended to demonstrate that that results obtained by MSKCC could be reproduced by other sites. FDA stated that the proposed study was inadequate to characterize the efficacy of ^{131}I-omburtamab; details were provided regarding expectations for a comparison to external control to estimate efficacy of ^{131}I-omburtamab. Protocol 101 was submitted on October 16, 2017.
12/19/2017	An Advice Letter was issued advising that the interpretation of **time-to-event endpoints in Study 101 will be difficult as it is a single-arm trial.** • **Interpretation of the data will be dependent on variables such as** the characterization of the external control, supportive data that confers anti-tumor activity (e.g. number of and duration of response), reproducibility between sites, toxicity and quality of the data collected.
3/26/2019	FDA again stated that time-to-event endpoints are difficult to interpret in the context of single-arm study. **The interpretation of the data will be dependent on variables such as the contemporaneous characterization of the external control, supportive data that confers anti-tumor activity (e.g., number of responses and duration of response), reproducibility between sites, toxicity, and quality of the data collected.**
9/11/2019	A CMC meeting was held to discuss product comparability data.
11/19/2019	Y-mAbs and FDA discussed clinical data that would be needed to support a BLA for ^{131}I-omburtamab. • **FDA stated that there are important limitations to the data provided from Study 03-133 such as the inability to isolate the treatment effect of ^{131}I-omburtamab from that of the other treatments administered for relapsed disease, that it is from a single-center, and that underlying differences in treatment or other disease-specific factors of the populations from the German registry and those from MSKCC may impact outcomes.** • **FDA also stated the importance of response data from a blinded independent review to support the efficacy evaluation of a marketing application.**
12/13/2019	In response to a proposal for accelerated approval submitted by Y-mAbs on November 22, 2019, FDA issued an Advice Letter reiterating that the **interpretation of any endpoint is dependent on the quality of the data submitted to define the populations treated in Study 03-133 and for the matched external controls**.
2/25/2020	Pre-BLA meeting. FDA stated that the **interpretation of the endpoints is dependent on the quality of the data submitted to define the populations treated in Study 03-133 and for the matched external controls.**

BTD = Breakthrough Therapy Designation; CMC = chemistry, manufacturing, and controls; CNS/LM = central nervous system and/or leptomeningeal; IND = Investigational New Drug application; MSKCC = Memorial Sloan Kettering Cancer Center;; PLI = Pre-License Inspection

Table 3: Regulatory Interactions Following the Initial BLA Submission

Date	Key Interactions
8/05/2020	Final submissions received to complete BLA submission.
10/02/2020	**FDA issued a RTF letter stating that application did not contain substantial evidence consisting of adequate and well-controlled investigations that ^{131}I-omburtamab is safe and effective for the treatment of pediatric patients with neuroblastoma that has relapsed to the CNS or LM**. FDA listed the following clinical reasons that the results of Study 03-133 did not support filing a BLA: • The treatment effect of ^{131}I-omburtamab cannot be objectively established or quantified based on the results from Study 03-133 compared to the reference rate derived from the CGCCR external control because there were no pre-specified statistical methods for matching analyses in place to assure comparability of the data from Study 03-133 to the CGCCR data. To provide a more accurate reference rate for 3-year overall survival (OS), **data from Study 03-133 and the external control should be reanalyzed using a propensity score adjusted analysis (i.e. matching or IPTW) for important baseline characteristics** (such as prior receipt of craniospinal irradiation) and prognostic factors (such as patient age and MYCN status). Additionally, to adequately interpret the analysis and ensure adequate event rate estimates, **it will be important for the external control data to reflect a patient population and follow-up to that is comparable to Study 03-133.** • Given the limitations associated with establishing and quantifying the treatment effect based on comparison of the 3-year OS rate observed in Study 03-133 to the 3-year OS rate derived from analyses of data from the CGCCR external control and from published literature, **direct evidence of the anti-tumor effect of ^{131}I-omburtamab through assessment of overall response rate and duration of response as determined by a blinded independent radiology is needed to provide supportive evidence of the effectiveness of ^{131}I-omburtamab** for the proposed indication.
11/03/2020	A Type A meeting was held to discuss the proposed plan to address filing issues described in the RTF letter. FDA expressed concern that the **CGCCR external control data may not be fit-for-purpose** as a direct comparator for the overall survival data from patients in Study 03-133 in that the patient populations may not be comparable**.** Specifically, there **appears to be an imbalance in receipt of radiation** treatment (more patients in the Study 03-133 received radiation, specifically craniospinal irradiation [CSI], compared to the patients in the CGCCR external control where no patients received CSI). FDA stated that given the uncertainties regarding the interpretation of overall survival results in Study 03-133, a single-arm study, **response data are needed** to support the antitumor effect of ^{131}I-omburtamab.
1/08/2021	A teleconference was held to discuss external control data that could serve as direct comparator to data in Study 03-133 and response data in Study 101. • FDA referenced communication to Y-mAbs from 1/07/2021 which expressed **concern that the CGCCR external control was not fit-for-purpose due to lack of granular patient-level data**. • FDA acknowledged that Y-mAbs had attempted to identify other sources including Children's Oncology Group and SIOPEN and that data on post-CNS relapse was not available. • Due to the difficulties associated with obtaining patient-level data that would be of sufficient quality and granularity to serve as an appropriate external control, Y-mAbs expressed a preference for pursuing a clinical development strategy based upon demonstration of durable overall responses in patients with measurable disease enrolled in Study 101.
3/26/2021	• A Type B meeting was held where FDA again expressed concern that insufficient information was provided determine whether the data from CGCCR are fit-for-purpose for establishment of a robust external comparator and outlined specific deficiencies. • FDA agreed to reassess the adequacy of the CGCCR external control after review of information provided in response to those deficiencies but stated that **if ultimately FDA cannot determine if**

Date	Key Interactions
	the patient populations are similar enough or if the sample size derived from the external control data is too small to make statistical comparisons, an alternative clinical development program will need to be discussed. • Additionally, FDA stated that given the uncertainty regarding the interpretability of overall survival results in Study 03-133, a single-arm study, **compelling response data will likely be needed to support the anti-tumor effect of ^{131}I-omburtamab, even if FDA determines that the data from the CGCCR external control are fit-for-purpose.**
6/01/2021	A Type B meeting where FDA stated that given the complexity of this external control study design and the uncertainty introduced by the retrospective use of historical data to design an external control arm to appropriately isolate the treatment effect as well as multiple prior looks at the data sources, • The review of a marketing application supported by the proposed comparative analysis will be based on **FDA's overall assessment of the results of multiple analyses, including analyses of the pre-specified primary and secondary endpoints in addition to sensitivity analyses.** • **FDA's determination regarding whether substantial evidence of effectiveness has been demonstrated will not rely solely on the results of a single analysis** of the primary efficacy endpoint or based on a single population.
9/14/2021	A Type B meeting was held where FDA expressed outstanding concerns regarding the datasets, definitions and derivations of the variables**. FDA also stated that they will not be able to rely on a single population or primary analysis and will consider the totality of evidence** from several sensitivity analyses to objectively quantify the treatment effect.
1/13/2022	A pre-BLA Type B meeting was held to discuss the plan to resubmit BLA 761176 based on the efficacy analyses using a propensity score model to evaluate OS in Study 03-133 compared with the external control group. • FDA stated that there was insufficient information to provide agreement on the efficacy package to support the BLA. • FDA stated that the ability to satisfactorily audit the CGCCR external control database for the external control cohort would be a filing issue. • Given the limitations of the external control cohort, FDA also strongly recommended submitting additional response rate data from Study 101 with the initial BLA submission. FDA **noted that the assessment of responses in Study 101 appear to be limited by the washout period from prior therapies relative to the timing of the baseline scans, and the timing of onset of response following ^{131}I-omburtamab, and that data from additional patients may strengthen the argument that there is a direct contribution from ^{131}I-omburtamab.**
3/21/2022	Y-mAbs agreed to follow up with a proposal for FDA to validate the data in the CGCCR external control dataset based on a potential audit de-identified records. Y-mAbs also agreed to submit details on the specific records that can be made available for validation. • On March 25, 2022, Y-mAbs provided additional detail regarding the audit process for the CGCCR external control dataset. • Y-mAbs stated they welcomed the opportunity to discuss the proposal in a teleconference the following week. • On March 29, 2022, FDA thanked Y-mAbs for the response and agreed to follow up within 30 days. **On March 31, 2022, Y-mAbs elected to resubmit the BLA prior to reaching agreement with the FDA on the content of the application.**

BLA = Biologics License Application; CNS/LM = central nervous system and/or leptomeningeal; OS = overall survival; FDA = Food and Drug Administration; PLI = Pre-license inspection; RTF = Refusal to File.

3 SUMMARY OF ISSUES FOR THE AC

3.1 EFFICACY ISSUES

- Issue #1: The external control population is not fit-for-purpose as a comparator due to substantive differences between the study and control populations that limit the ability to attribute survival differences to the effect of ^{131}I-omburtamab.
- Issue #2: Recognizing the level of evidence provided and need for regulatory flexibility, FDA performed additional analyses to examine bias and results reinforce that differences in survival cannot be reliably attributed to ^{131}I-omburtamab.
- Issue #3: The application does not include reliable response rate data to provide supportive evidence of the treatment effect of ^{131}I-omburtamab.

3.1.1 Sources of Data for Efficacy

The Applicant is seeking approval based on overall survival results from an investigator-initiated, single-arm single-center trial, Study 03-133, compared to an external control derived from the Central German Childhood Cancer Registry (CGCCR) and supportive data from Study 101 (Table 4).

Table 4: Overview of Clinical Trials

Trial ID	Objectives	Trial Population	Number of Patients with Neuroblastoma	Status
03-133 Single-center	Primary: • Define clinical toxicities of ^{131}I-omburtamab Key Secondary: • OS at 3 years (primary efficacy endpoint)# • CNS/LM PFS at 12 months • Duration of follow-up	Patients with a histologically confirmed diagnosis of an ^{131}I-omburtamab reactive malignancy with CNS/LM disease	Total: 109 Treated at proposed recommended dose: 94 PK/Dosimetry: 27	Initiated: February 2004; Enrollment closed July 2019
101 Multi-center	Primary: • OS at 3 years Main Secondary: • Estimated OS at 12 months • CNS/LM PFS at 6 and 12 months • ORR at 6 months • PK and dosimetry • Assess safety • Evaluate immunogenicity	Patients between birth and 18 years of age with histologically confirmed diagnosis of neuroblastoma with relapse in the CNS or LM.	Total: 50 Safety data available for at the time of the BLA submission: 32 PK/Dosimetry: 25	Initiated December 2018 Ongoing

#Study 03-133 was initially designed to evaluate the maximum tolerated dose of ^{131}I-omburtamab. The key secondary objective of OS at 3 years was added to the protocol in Amendment 25 and is the primary efficacy endpoint for this BLA.

OS=overall survival, ORR=overall response rate, PFS=progression-free survival, PK=pharmacokinetics, CNS=central nervous system, LM=leptomeningeal, BLA=biologics license application

Study 03-133

Study 03-133 is a single-arm, single-center, dose-finding and dose-expansion trial conducted at MSKCC that included pediatric patients with neuroblastoma with relapse in the CNS including parenchymal or LM metastases. Patients with rapidly worsening neurological status and obstructive or symptomatic communicating hydrocephalus were ineligible. Patients received ^{131}I-omburtamab as an intracerebroventricular infusion at a dose based on age. At the discretion of the investigator, patients were eligible to receive a second dose of ^{131}I-omburtamab 5 weeks after the first dose in the absence of disease progression or unacceptable toxicity. Patients received a multi-modality therapy regimen (including CNS-directed surgery, chemotherapy, and/or radiotherapy) before entering the screening period.

The trial was initiated on February 5, 2004 with the first patient enrolled in July, 2004 and enrollment closed in December 2018. This trial was not originally intended to provide evidence of efficacy, with an initial planned enrollment of only 30 patients in the original protocol; however, additional patients were enrolled as part of a dose-expansion component that was subsequently added to the protocol. In total, 94 patients with neuroblastoma with CNS/LM metastases were treated at the proposed recommended age-based dosage of 25 mCi, 33.5 mCi, or 50 mCi. Among these patients, the median age at time of consent was 4.8 years (range: 0.9 – 13 years), 69% were male, 78% were White, 10% were Black or African American, 3.2% were Asian, and 10% race was either unknown or not reported. Sixty percent of these patients had no prior relapses, 32% had 1 prior relapse, 4.3% had 2 or more prior relapses, and in 4.3% the number of prior relapses was not known. At CNS relapse, 63% of patients had parenchymal metastases only, 9% had LM only, 7% had both parenchymal metastases and LM, and 21% were not reported. Relapse was limited to the CNS in 70% of patients, included both the CNS and systemic relapse in 28%, and was not reported in 2.1%. All patients received CNS-directed therapy prior to treatment with ^{131}I-omburtamab, including surgery (83%), chemotherapy (98%), and radiotherapy (93%). The majority (76%) of patients received all three treatment modalities.

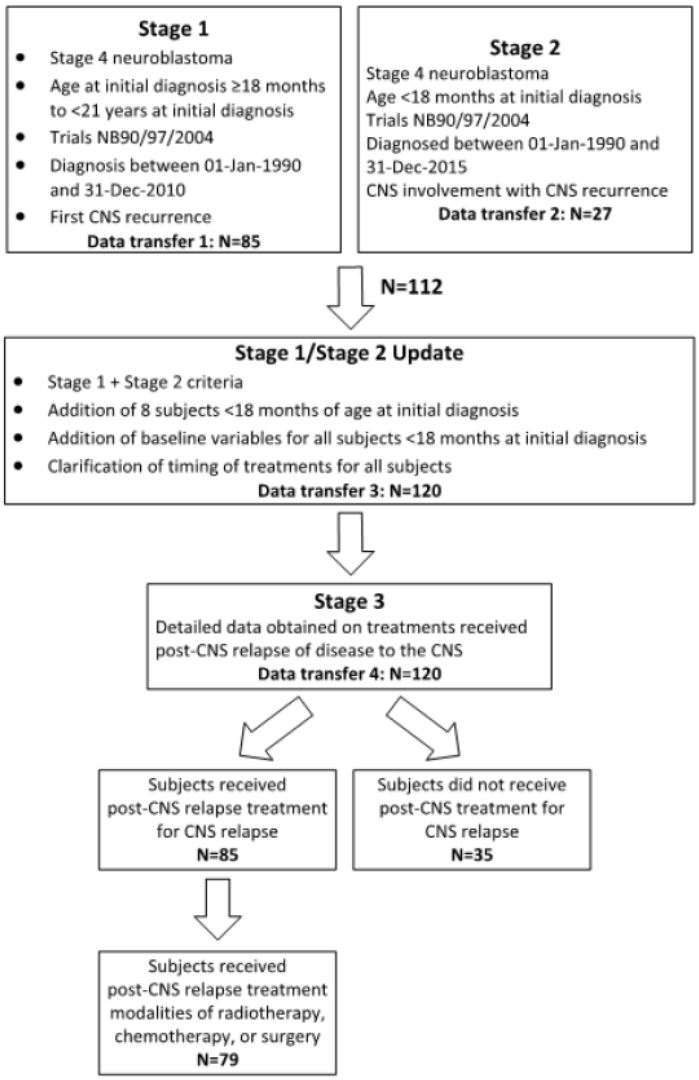
To support this application, the Applicant submitted an interim study report with efficacy data collected through March 12, 2020 in 107 patients with relapsed neuroblastoma with CNS/LM metastases. The major efficacy outcome measure for the interim report was OS landmark rate at 3 years. To provide context for the survival data, the Applicant compared the patients in Study 03-133 to an external control (described below). The primary analysis includes Kaplan-Meier estimates and corresponding 95% CIs. Secondary endpoints included landmark CNS/LM PFS rates. Although ORR was included as a secondary endpoint in the study, no results were included in the interim report due to incomplete collection of response data.

External Control Data from the CGCCR

The Central German Childhood Cancer Registry (CGCCR) was established in 1980 and hosted by the Institute of Medical Biostatistics, Epidemiology and Informatics at the University Medical Center of the Johannes Gutenberg University Mainz. The CGCCR registers about 1,800 cases per year from all pediatric oncology centers affiliated with the Society for Pediatric Oncology and Hematology and the national trial office for neuroblastoma in Cologne. It is estimated that more than 95% of all German children and adolescents under the age of 15 years with malignant diseases are reported to the CGCCR. The data from CGCCR used as the source population for the external control arm includes patients who

were originally diagnosed with neuroblastoma between 1990 and 2015 (1990-2010 for patients ≥18 months to <21 years and 1990-2015 for patients <18 at initial diagnosis). The selection algorithm for the external control population is described in Figure 1.

Figure 1: Patient Selection Process for the CGCCR External Control Population



Source: Y-mAbs External Control Arm (ECA) Report, Version 1.0; Page 19; Submitted March 31, 2022

Patients enrolled in Study 03-133 received different modalities of treatment for CNS relapse, including radiation, chemotherapy and/or surgery prior to start of ^{131}I-omburtamab therapy. A total of 120 patients with neuroblastoma were identified from the CGCCR with CNS relapse. Of these, 85 patients received any post-CNS-relapse anti-cancer therapy. To improve comparability of treatment patterns between the Study 03-133 and external control populations, the 79 patients who received at least one post-CNS relapse treatment modality (radiotherapy, chemotherapy, or surgery) were selected. Additional modality groups proposed by the Applicant are described in Table 6 in the section below entitled “Analysis of Efficacy Comparing Study 03-133 to External Control”.

Study 101

Study 101 is an ongoing single-arm, multi-center trial in pediatric patients with neuroblastoma with CNS/LM disease. The first patient was treated on December 11, 2018. As of the February 1, 2022 data cut-off, 50 enrolled patients had received treatment with ^{131}I-omburtamab.

The primary efficacy endpoint is OS landmark rate at 3 years. The primary analysis includes Kaplan-Meier estimates and corresponding 95% CIs. Secondary endpoints included landmark CNS/LM PFS rates at 6 and 12 months and ORR. An interim analysis was planned based on enrolled patients who received at least one dose of study drug before January 1, 2020.

3.1.2 Efficacy Summary

Analysis of Efficacy Comparing Study 03-133 to the External Control (CGCCR)

The goal of this comparison is to quantify the treatment effect of ^{131}I-omburtamab based on the results of Study 03-133 using external data from the CGCCR repository, taking into account that time to event endpoints such as OS are uninterpretable in single-arm trials and the high proportion of patients in Study 03-133 who received CNS-directed treatment including radiotherapy prior to ^{131}I-omburtamab treatment. The criteria used to define the populations used for comparison are described in Table 5.

Table 5: Eligibility Criteria for Comparative Analysis Populations

Study 03-133	External Control (CGCCR)
Patients must have a histologically confirmed diagnosis of a malignancy known to be ^{131}I-omburtamab reactive. Antigen expression must be confirmed by immunohistochemical staining of tumor and assessed by the Department of Pathology or by immunofluorescence of bone marrow except for patients confirmed to have neuroblastoma.	Stage 4 neuroblastoma
Patients must have CNS/leptomeningeal disease which is refractory to conventional therapies or for which no conventional therapy exists OR a recurrent brain tumor with a predilection for leptomeningeal dissemination (medulloblastoma, PNET, rhabdoid tumor).	CNS disease at first recurrence or with initial CNS involvement
Patients must have not have a rapidly progressing or deteriorating neurologic examination.	No information on clinical status or disease trajectory provided. The Applicant states this is mitigated by excluding patients without post relapse treatment from analyses.
Both pediatric and adult patients of any age are eligible.	0-20 years

Study 03-133	External Control (CGCCR)
Exclusion Conditions: Patients who have received CSI less than 3 weeks prior to the start of this protocol. Patients who have received systemic chemotherapy (corticosteroids not included) less than 3 weeks prior to the start of this protocol.	In Germany, CSI is not used for treatment in children.

CNS = central nervous system; CSI = craniospinal irradiation; PNET = primitive neuroectodermal tumor.
Source: Modified from Y-mAbs External Control Arm (ECA) Report, Version 1.0; Page 16; Submitted March 31, 2022

Methods

The Applicant proposed to use certain clinically important baseline covariates to build the propensity score model for comparison of Study 03-133 to the external control arm. The propensity score model only included baseline variables with no missing data or limited missing data (defined as ≤15%). The comparative statistical analysis was conducted using complete cases only (patients with missing data were excluded).

The proposed estimand for causal effect estimation was average treatment effect on the treated (ATT) by weighting (Morgan, 2008). Due to the imbalance in sample size, the Applicant proposed down-weighting of the external control arm. The Applicant also proposed trimming of large weights (>5) for stabilization. Although FDA communicated to the Applicant that the proposed down-weighting of the external control arm appeared arbitrary, the Applicant retained this down-weighting scheme in the statistical analysis plan.

In order to improve the comparability of the distribution of post CNS-relapse treatments of the external control population to the trial population, the Applicant proposed a series of modality groups based on the types of post-CNS relapse therapies received. A summary of the modality groups within each patient population is provided in Table 6.

Table 6: Modality Groups in Study 03-133 and the CGCCR External Control Comparator

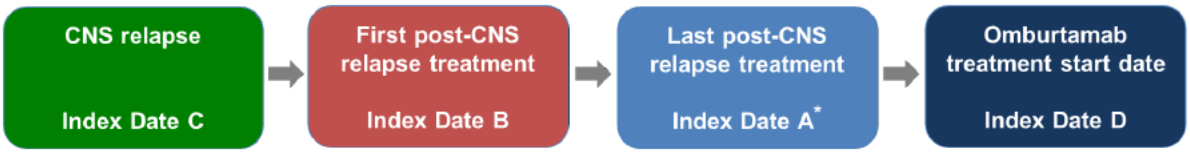
Group	Treatment Modalities Received	Study 03-133 (n=94)*	External Control (n=79)
Group 1	Received at least one post-relapse therapy (surgery, radiation, or chemotherapy)	94 (100%)	79 (100%)
Group 2	Received post-relapse radiation therapy and at least one other therapy (surgery or chemotherapy)	86 (91%)	35 (44%)
Group 3	Received post-relapse radiation therapy, surgery, and chemotherapy	71 (76%)	21 (27%)
Group 4	Received post-relapse radiation therapy	87 (93%)	40 (51%)

*For Study 03-133, the Applicant's efficacy population included 107 patients. However, FDA considers the efficacy population to include only the 94 patients who were treated at the proposed recommended age-based dose of 25 mCi, 33.5 mCi, or 50 mCi.

Note: The Applicant considers the primary analysis population to consist of 89 patients from Study 03-133 and 34 patients from the external control in Modality Group 2 who had complete case data. The FDA considers the primary analysis population to consist of 77 patients from Study 03-133 and 34 patients from the external control in Modality Group 2 who had complete case data.

Due the variability in the receipt and timing of post-CNS relapse therapies, the Applicant also proposed several index dates for the analysis, which are shown in chronological order in Figure 2.

Figure 2: Index Dates proposed by the Applicant



* Index Date A is defined as the start date of last type of post-CNS relapse modality (radiotherapy, chemotherapy, or surgery)

The Applicant's proposed primary analysis was conducted in patients from Modality Group 2 using Index Date A for both groups based on a complete case analysis, resulting in a sample size of 89 patients from Study 03-133 and 34 patients from the external control. The Applicant also specified multiple sensitivity analyses considering various combinations of modality groups and index dates with and without imputation for missing covariates.

For the primary and sensitivity analyses, overall survival was estimated and compared between the two groups with 3-year survival rates also described by groups. The same weighting approach, ATT weighting by propensity scores between Study 03-133 and external control, was used for all analyses. The availability of baseline covariates was dependent on the choice of index date as summarized in Table 7.

Table 7: Baseline Covariates by Index Dates

Covariate	Index Dates at which Covariate can be included in a Propensity Score Model
Age at neuroblastoma diagnosis	A/D, B, C
MYCN Status	A/D, B, C
Time from neuroblastoma diagnosis to CNS relapse	A/D, B, C
Time from CNS relapse date to the start of post-CNS relapse treatments	A/D, B
Post-CNS chemotherapy initiated on or before Index Date A*	A/D
Post-CNS surgery initiated on or before Index Date A	A/D
Number of post-CNS treatments initiated on or before Index Date A	A/D

* Available at Index Date A, but not included in propensity score model

Results

FDA conducted analyses based on the Applicant's proposed methodology but restricting the population for Study 03-133 to include only the 94 patients treated with ^{131}I-omburtamab at the recommended dose of 50 mCi (or the appropriate age-adjusted dose). Table 8 provides the demographic and clinical characteristics for patients in Modality Group 2 by treatment group before and after weighting.

Table 8: Demographic and Clinical Characteristics for Modality Group 2

Covariate	Before Weighting		After Weighting	
	Study 03-133 (n=86)	External Control (n=35)	Study 03-133 (n=77)*	External Control (n=24.8)*
Age at neuroblastoma diagnosis in years, median (range)	2.6 (0.03, 12.1)	2.4 (0.1, 17.4)	2.5 (0.2, 9.7)	1.4 (0.1, 24.9)
MYCN status Amplified Not amplified Not reported	 56% 34% 10%	 51% 46% 2.9%	 62% 38% 0%	 55% 45% 0%
Time from neuroblastoma diagnosis to CNS relapse in months, median (range)	17.6 (0, 79.8)	21.6 (9.2, 58.1)	17.7 (0, 61.7)	16.8 (1.0, 32.6)
Time from CNS relapse to the start of first post-CNS relapse treatment in days, median (range)	6 (0, 67)	8 (1, 94)	6 (0, 67)	5.4 (0.1, 18.2)
Post-CNS relapse chemotherapy	99%	89%	99%	99%
Post-CNS relapse radiation therapy	100%	100%	100%	100%
Post-CNS relapse surgery	84%	71%	83%	83%
Number of post-CNS relapse treatment modalities received on or before Index Date A 2 3	 17% 83%	 40% 60%	 18% 82%	 18% 82%

*Weighted sample size for complete case analysis

Table 9 provides the results from analyses utilizing Modality Group 2 based on two sets of index dates: 1) Index Date A for both arms (the Applicant's primary analysis), and 2) Index Date D for Study 03-133 and Index Date A for the CGCCR external control arm (a sensitivity analysis). For both analyses, the propensity score model included the following covariates: age at neuroblastoma diagnosis, MYCN status, time from neuroblastoma diagnosis to CNS relapse (square root transformation), time from CNS

relapse date to the start of post-CNS relapse treatments, post-CNS Surgery initiated on or before Index Date A, and number of post-CNS treatments (radiotherapy, chemotherapy and surgery) initiated on or before Index Date A. Per the Applicant, the variable post-CNS chemotherapy initiated on or before the index date was not included in the propensity score model due to the extremely small number of subjects without the treatment in Study 03-133. The complete case analysis included 34 patients in Modality Group 2 of CGCCR external control dataset and 77 patients in Study 03-133 who were treated at doses of 25 mCi, 33.5 mCi, or 50 mCi based on age.

Table 9: Analysis of Overall Survival based on Modality Group 2

	Index Date A for CGCCR Group Index Date A for Study 03-133		Index Date A for CGCCR Group Index Date D for Study 03-133	
	Study 03-133	External Control	Study 03-133	External Control
Weighted sample size, N	77.0	24.8	77.0	24.8
Median, months (95% CI)	36.7 (24.6, 66.8)	15.8 (5.4, 28.6)	31.3 (20.2, 57.6)	15.8 (5.4, 28.6)
3-year OS rate, % (95% CI)	50 (38, 61)	31 (14, 49)	48 (36, 59)	31 (14, 49)
Hazard ratio (95% CI)	0.62 (0.32, 1.20)		0.69 (0.37, 1.30)	

However, upon review of the proposed external control data, FDA identified confounding factors and additional sources of bias that were not adjusted for in the Applicant's primary analysis. The section below describes the confounding factors and additional sources of bias in the above analyses comparing differences in survival between Study 03-133 and the external control that preclude the ability to quantify a treatment effect for ^{131}I-omburtamab using the data provided in this application.

3.1.3 Efficacy Issues in Detail

Issue #1: The external control population is not fit-for-purpose as a comparator due to substantive differences between the study and control populations that limit the ability to attribute survival differences to ^{131}I-omburtamab.

There are fundamental differences in the clinical trial and external control populations, particularly with regard to receipt of CNS-directed therapies for CNS/LM disease. FDA approval requires substantial evidence of effectiveness to be established. In specific circumstances, this may rely on one adequate and well-controlled trial and confirmatory evidence. This adequate and well-controlled trial may rely on an external control, however regulations require that this rely on "comparable patients or populations" (21 CFR 314.126).

Prior to receipt of ^{131}I-omburtamab, most patients in Study 03-133 received a multi-modality treatment regimen, as described in Table 10.

Table 10 : Suggested treatment paradigm prior to receipt of ^{131}I-omburtamab*

Time	Suggested Pre-treatment for Study 03-133 and Study 101
Week -12	**Resection** of CNS disease when possible
Week -11	**Irinotecan** 50 mg/m^2/dose IV daily x5
Week -10	**Craniospinal irradiation** 1800-2160 cGy + boost at tumor bed to 3000 cGy
Week -5	**Irinotecan** 50 mg/m^2/dose IV daily x5
	Temozolomide 250 mg/m^2/dose daily x5
	Carboplatin 500 mg/m^2/dose daily x2 (if systemic disease present)
	Stem cell rescue if necessary
Study start	^{131}I-omburtamab administration

*Represents the general treatment paradigm for Study 03-133, but was only protocol-specified for Study 101.

Analysis of Study 03-133 and external control populations revealed a clear imbalance in post-CNS relapse therapies received by each group including radiation therapy (Table 11) and chemotherapy (Table 12).

Table 11: Comparison of post-CNS relapse CNS-directed radiation therapy in Study 03-133 and External Control Modality Group 1

	Study 03-133 (n=94)	External Control (n=79)
Proportion receiving radiation therapy post-CNS relapse	93% (prior to ^{131}I-omburtamab)	51%
Time from relapse to first radiation therapy, median	21 days (3, 688)	61 days (3, 414)
Other known radiation therapy characteristics	91% of patients received craniospinal irradiation (18 or 21 Gy +/- boost)	No patient received craniospinal irradiation No further details on type/dose of RT available

Table 12: Comparison of post-CNS relapse chemotherapy in Study 03-133 and External Control Modality Group 1

	Study 03-133 (n=94)	External Control (n=79)
Proportion receiving chemotherapy post-CNS relapse	98% (prior to ^{131}I-omburtamab)	85%
Other known chemotherapy characteristics	Most patients received temozolomide/irinotecan	Most patients received topotecan/etoposide Few received temozolomide (6%) or irinotecan (5%)

In addition to these known differences in treatments, the non-randomized comparison of the single-center, single-arm Study 03-133 to the CGCCR-derived external control may result in clinically important and prognostic unknown differences between the populations. Among other issues, lack of randomization can increase concern for unmeasured confounding which is an additional threat to study validity. For example, the lack of protocol-specified recommendations for treatment of CNS/LM relapse for the CGCCR population may introduce additional bias since patients in the CGCCR dataset may not necessarily have been able to tolerate multi-modality therapy. Additionally, post-^{131}I-omburtamab treatment was not systematically captured in Study 03-133. Based on typical US treatment practices, it is likely that many patients in Study 03-133 received additional therapy following ^{131}I-omburtamab which could contribute to longer survival; interim data from the supportive study (Study 101) indicate that 34 of 50 (68%) of patients received concomitant anti-cancer therapy (chemotherapy, immunotherapy, radiotherapy, surgery, or a combination of both) after ^{131}I-omburtamab.

Furthermore, there may be factors specific to the single trial center that may affect survival (e.g. ability to travel to the trial site) and unknown differences in clinical care between the United States and Germany.

Issue #2: Recognizing the level of evidence provided and need for regulatory flexibility, FDA performed additional analyses to examine bias and results reinforce that differences in survival cannot be reliably attributed to ^{131}I omburtamab.

Several major sources of bias were identified and are enumerated below, along with FDA's approach to address these biases.

Population Selection: Among other differences in these populations, differences in the receipt of post-CNS relapse treatment between the Study 03-133 and external control populations appears to affect survival. Overall, patients enrolled in Study 03-133 (n=94) received more intensive treatment compared to patients in the external control population (n=79), both in terms of number and types of post-CNS relapse treatments. The Applicant identified modality groupings to better identify a comparable

population for Study 03-133 (Table 6). Modality Group 3 likely represents the most comparable population but has an extremely limited sample size. Thus, after discussion with the FDA, Modality Group 2 was selected by the Applicant for the primary analysis as it was the most pragmatic modality group balancing population comparability and sample size. Analysis of survival for the external control based on modality groupings suggests that survival is affected by the number of treatments received (Table 13).

Table 13: Survival in CGCCR external control based on modality grouping

Group	Modality	Study 03-133 (n=94)	External Control (n=79)	External Control Median Survival* (months)
Group 1	Received at least one post-relapse therapy	94 (100%)	79 (100%)	9.9 (95% CI: 6.9, 14.0)
Group 2	Received post-relapse radiation therapy and at least one other therapy (surgery or chemo)	86 (91%)	35 (44%)	16.0 (95% CI: 10.0, 29.8)
Group 3	Received post-relapse radiation therapy, surgery, and chemotherapy	71 (76%)	21 (27%)	29.8 (95% CI: 11.7, NE)

NE = Not Evaluable

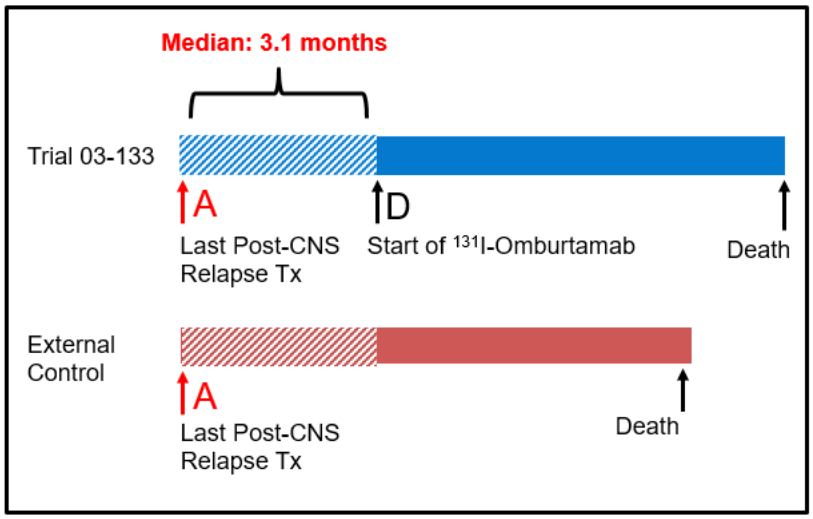
* Survival defined as the time from CNS relapse to death or last known date alive.

Immortal Time (Credited Survival): The Applicant chose Index Date A (start of last type of post-CNS relapse treatment) for both arms for the primary analysis, but it is unclear if this is the most appropriate index date. Each of the four proposed index dates (Figure 2) have limitations with respect to analysis and interpretation. The modality groups were defined based on the type and the number of post-relapse therapies and were not redefined for each index date. As such, using Index Date C, starting at CNS relapse, or Index Date B, starting at initiation of first post-relapse therapy, would make any post-relapse treatment a post-baseline therapy or an intercurrent concomitant treatment. For Index Date A or D, all therapies initiated between CNS relapse and the index date are available as baseline covariates making the modality groups most relevant for these index dates. However, the use of index dates that require survival for a period of time after the index date until the date of administration of ^{131}I-omburtamab for inclusion in the analysis population may raise concerns of immortal time bias, as described below.

Index date D, which is the start of ^{131}I-omburtamab treatment, is available only for Study 03-133. The most appropriate corresponding index date for the CGCCR external control arm is Index Date A, but this results in a concern of immortal time bias. Specifically, in Study 03-133, a patient that died between Index Dates A and D would not have received ^{131}I-omburtamab treatment, and therefore would not be included in the study population. However, patients in the external control group were not required to have survived for any length of time after Index Date A, resulting in the inclusion of patients from the external control group with shorter survival times than patients from Study 03-133.

To illustrate the effect of this point, in Study 03-133, the median time between Index Date A and Index Date D (Immortal Time) was 3.1 months (range 0.6 to 30 months). In the external control, among 79 patients who received any post-CNS relapse therapy (surgery, chemotherapy, or radiation therapy), 24 patients (30%) died within 3.1 months of Index Date A (Figure 3). This subset may represent patients who may have been excluded from the opportunity to enroll in Study 03-133 due to immortal time bias. Use of Index Date D in the Study 03-133 population and Index Date A in the external control population (Index Dates A/D) provides an understanding of how immortal time bias affects the primary analysis. Additionally, this analysis provides a more conservative comparison by ensuring that the index date for the Study 03-133 population is the last date that patients were required to be alive.

Figure 3: Immortal Time Bias Related to Index Date Selection



Study Time Period Differences*:* Although there is overlap, there are differences in the temporal periods of the CGCCR external control and Study 03-133. Patients in the CGCCR were accrued over a period of 25 years, from 1990 until 2015, while Study 03-133 began enrollment in 2004, with the first patient treated at the proposed recommended dose diagnosed with CNS relapse on September 21, 2005. Due to evolution of standard of care and supportive care over time, FDA and the Applicant performed analyses to determine if survival outcomes have changed over time in the CGCCR external control arm. Table 14 provides the frequency distribution of patients in Study 03-133 and the CGCCR external control, as well as the median survival of patients diagnosed with CNS relapse before and contemporaneous to Study 03-133. The results indicate that OS appears to improve for patients with more recent dates of CNS relapse.

Table 14: Survival in CGCCR external control based on era of therapy.

Era of Therapy	Study 03-133 (n=94)	External Control (n=79)	External Control Median Survival (months)*
Before Study 03-133 (1990-2005)	-	44 (56%)	9.6 (95% CI: 5.6, 11.7)
Contemporaneous** (2005-present)	94 (100%) 2005-2018	35 (44%) 2005-2020	15.7 (95% CI: 5.3, 29.8)

*Survival defined as the time from CNS relapse to death or last known date alive.
**CNS relapse occurring on or after September 21, 2005

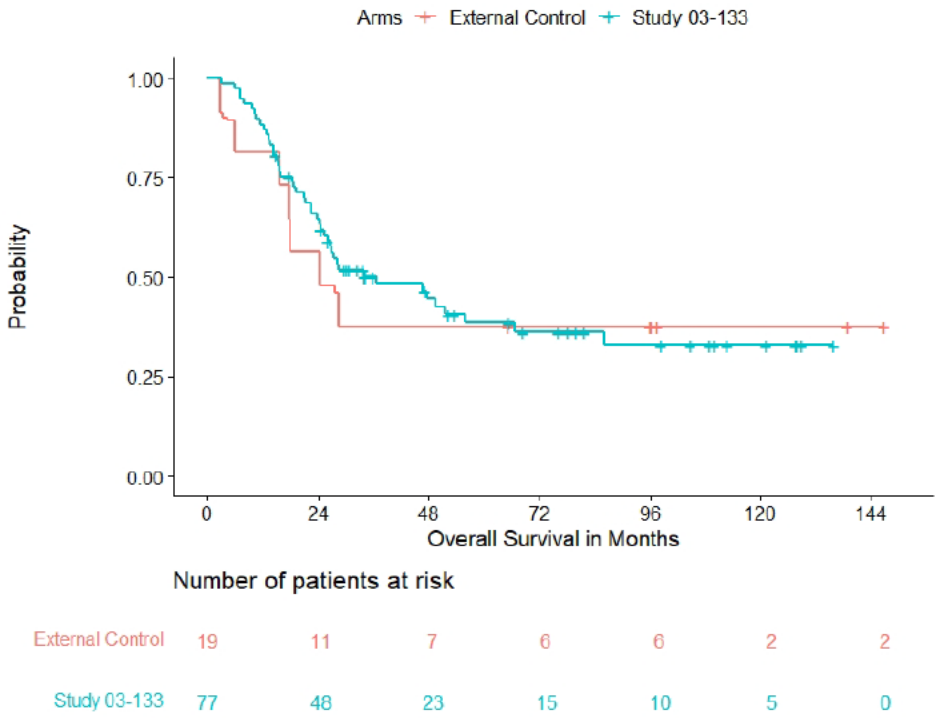
FDA approach to mitigating bias: FDA's initial analysis, which is similar to the Applicant's primary analysis with the exception of restricting the Study 03-133 analysis population to those patients with the proposed recommended intended dose, is described in the preceding section and enumerated in Table 9. In addition to these results, FDA performed sensitivity analyses adjusting for era of treatment to control for observed temporal bias described above. Table 15 and Figure 4 present sensitivity analyses comparing OS in Study 03-133 and the external control using Modality Group 2, restricting era of treatment, and adjusted by propensity score-based weighting. This analysis utilized the Applicant's proposed index date (Index Date A).

Table 15: Survival analysis of Study 03-133 and CGCCR external control using Modality Group 2 and restricting era of therapy

	Study 03-133	External Control
Index Date used	A	A
Weighted sample size, N	77.0	19.3
Median, months (95% CI)	36.7 (24.6, 66.8)	24.4 (6.0, NE)
3-year OS rate, % (95% CI)	50 (38, 61)	38 (14, 62)
Hazard ratio (95% CI)	**0.91 (0.41, 2.02)**	

NE = Not Evaluable

Figure 4: Kaplan-Meier plot comparing Study 03-133 and CGCCR external control using Modality Group 2 restricting era of therapy

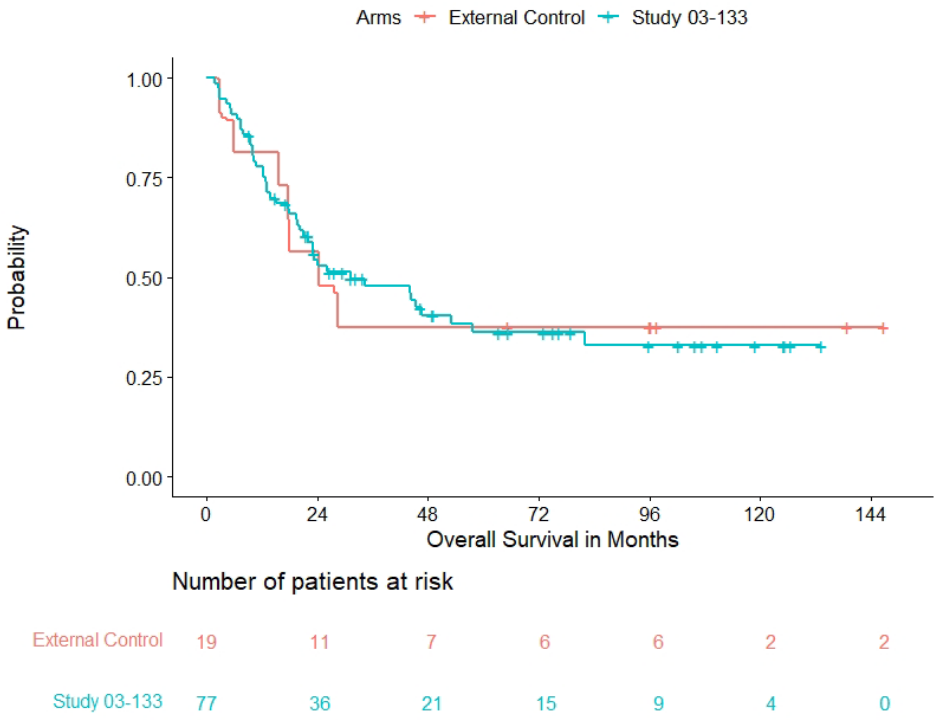


The analyses were also performed using Index Date A (CGCCR)/D (Study 03-133) to illustrate and adjust for the effect of immortal time bias. Survival analyses described in Table 16 and Figure 5 demonstrate the comparison of Study 03-133 and CGCCR using Modality Group 2 and restricting for era of treatment, adjusted by propensity score-based weighting, and using Index Dates A/D.

Table 16: Survival analysis of Study 03-133 and CGCCR external control using Modality Group 2, restricting era of therapy, and using Index Dates A/D

	Study 03-133	External Control
Index Date used	D	A
Weighted sample size, N	77.0	19.3
Median, months (95% CI)	31.3 (20.2, 57.6)	24.4 (6.0, NE)
3-year OS rate, % (95% CI)	48 (36, 59)	38 (14, 62)
Hazard ratio (95% CI)	**1.02 (0.48, 2.16)**	

Figure 5: Kaplan-Meier plot comparing Study 03-133 and CGCCR external control Modality Group 2, restricting era of therapy, and using Index Dates A/D



In general, given the small sample sizes of Study 03-133 and the external control cohort, survival estimates such as Kaplan-Meier medians or 3-year OS rates may not be reliable. This may be particularly true with analyses in smaller subgroups of patients which improve comparability of the subpopulations but also result in smaller sample sizes for analysis. Nevertheless, adjusting for modality group, treatment era, and index date appears to minimize the observed differences in overall survival between Study 03-133 and the external control group and highlights the relevance of the identified sources of confounding and other bias.

It is important to note that these sensitivity analyses do not adjust for other important known differences in types of radiation received (the majority of patients in 03-133 received CSI, compared to zero patients in the external control group), types of chemotherapies, numbers of lines of treatment prior to receipt of ^{131}I-omburtamab. They also do not adjust for potentially important unknown differences, such as treatments received by patients in Study 03-133 following ^{131}I-omburtamab and differences in population selection related to geography (US versus Germany), amongst others.

Issue #3: Lack of response rate data to support the activity of ^{131}I-omburtamab in CNS/LM relapsed neuroblastoma.

Study 101 provided the opportunity to support efficacy claims of ^{131}I-omburtamab with systematic tumor assessments that were unavailable in Study 03-133. In Study 101, tumors were assessed by MRI at 5-, 10-, and 26-weeks after the first dose of ^{131}I-omburtamab and evaluated by a blinded independent

central review (BICR). RANO group criteria for brain metastasis were used to assess parenchymal disease; these criteria require confirmation of response by a second imaging assessment obtained at least 4 weeks following the first image documenting a response (Lin 2015). EANO-ESMO guidelines were used to assess response for LM metastases (Le Rhun 2017).

Multi-modality CNS-directed therapy was protocol-specified (Table 10) post-CNS relapse and prior to receiving ^{131}I-omburtamab. Given these multiple pre-treatments, patients had minimal CNS disease at baseline prior to receiving ^{131}I-omburtamab. Forty-seven of 48 patients (98%) with CSF cytology available had negative cytology at baseline. Furthermore 30 of 50 patients (60%) had no evidence of disease in the CNS per BICR.

Per BICR assessment, the Applicant reported 7 responses; however, 3 of these responses were not confirmed by subsequent imaging following initial documentation of response, including 3 of the 5 reported responders with parenchymal disease. FDA considers durability of response a critical component of response assessment and confirmation of response on follow-up imaging provides assurance regarding consistency of interpretation of response (which is particularly important when responses are difficult to assess, such as with LM metastases) and an assessment of the clinical importance of the response since transient responses are not likely to be meaningful.

With respect to assessment of disease at baseline, per EANO-ESMO diagnostic criteria, a "confirmed" diagnosis of leptomeningeal disease requires CSF analysis and positive cytology (Le Rhun 2017). Diagnosis based on imaging alone may be considered either probable or possible based on the presence of clinical signs. In Study 101, 98% of patients with LM disease had negative CSF cytology results prior to receipt of ^{131}I-omburtamab, including the two patients with reported responses in leptomeningeal disease, which limits conclusions about efficacy. EANO-ESMO guidelines incorporate clinical status, cytology and imaging (as defined as improved, stable, or worse) to define a response for patients with LM metastases. For patients in Study 101 with LM, there is insufficient information in most cases to assess response as patients lacked clinical information and baseline positive CSF cytology to meet diagnostic criteria for "confirmed" or "probable" LM to assess for a response.

FDA review of BICR results and patient narratives revealed additional issues with each reported confirmed response that limits their interpretability (see Appendix Table 1):

- 1 of 2 patients with parenchymal disease had no measurable target lesions, again limiting the ability to interpret the response data; additionally, the second reviewer did not identify any CNS/LM disease in this patient. The second patient with parenchymal disease also had LM disease per one reviewer but no evidence of CNS or LM disease by the second reviewer.

- Limited washout seen in two of the reported responders also affects the ability to interpret these results. Specifically, in these patients it may not be possible to isolate the treatment effect of ^{131}I-omburtamab from these other treatments. Two of 4 responders received radiation therapy within 30 days of their baseline Although this was acceptable according to eligibility criteria, clinically, treatment-related effects from radiation can appear from a few weeks to months after radiation (Smart D, et al, 2017). One of these 2 patients who received radiation therapy within 30 days of their baseline scan also received chemotherapy within 21 days of their baseline scan, which was a protocol violation per Study 101 exclusion criteria. This is

compounded by receipt of chemotherapy or immunotherapy during the interval between first scan demonstrating a reported response and the subsequent scan used for confirmation in 3 of 4 patients. This included two patients who received temozolomide, which is thought to have activity in patients with neuroblastoma and CNS relapse. This subsequent therapy limits the ability of these reported responses to be considered "confirmed" and the ability to attribute treatment effect to ^{131}I-omburtamab.

- Finally, there was disagreement between the primary radiology reviewers in all cases, requiring adjudication. In two cases there was a major disagreement. This included one case with a reported partial response that the secondary reviewer reported as no evidence of disease at baseline and progressive disease at 5, 10, and 26 weeks. In another case with a reported complete response, the secondary reviewer reported no evidence of disease at baseline, 5 weeks, and 10 weeks and progressive disease at 26 weeks. Although these discrepancies were adjudicated, they provide further concerns regarding the reliability and reproducibility of the study results.

Overall, no patient in Study 101 demonstrated an unequivocal treatment response that could be definitively attributed to ^{131}I-omburtamab.

3.2 SAFETY ISSUES

3.2.1 Sources of Data for Safety

The FDA safety evaluation focused on data from pediatric patients with a histologically confirmed diagnosis of neuroblastoma with CNS/LM relapse enrolled in Study 03-133 (n=94, data cutoff February 1, 2022) and Study 101 (n=32, data cutoff June 1, 2022) who received ^{131}I-omburtamab at the proposed recommended dose based on patient age (25 mCi, 33.5 mCi, or 50 mCi). The application 120-day safety update included data from 18 additional patients in Study 101, which was generally consistent with previously submitted information, with the exception of one new case of papillary thyroid cancer reported as a secondary malignancy.

Notably, the safety population used in the Applicant's safety analyses comprises 109 patients from Study 03-133 (which includes patients who received ^{131}I-omburtamab at doses below and above the recommended age-based dose) and 50 patients from Study 101.

3.2.2 Safety Summary

The key safety concerns for ^{131}I-omburtamab include risks associated with placement and use of an Ommaya-like reservoir, risk of radioactive iodine causing off-target effects, and adverse reactions associated with treatment with the drug including radiation exposure (including risk of secondary malignancy), myelosuppression, chemical meningitis, infusion-related reactions and neurotoxicity.

In order to receive ^{131}I-omburtamab, patients must be well enough to undergo a surgical procedure to have an Ommaya catheter placed. Risks for Ommaya catheter placement include catheter migration in the newly placed setting requiring surgical revision, reservoir infection which may lead to catheter revision, technical failure of the device requiring surgical correction, CSF leakage, and bleeding.

Treatment with ^{131}I-omburtamab contributes to a patient's overall long-term radiation exposure and cumulative radiation exposure is associated with an increased risk for cancer. Though patients treated were heavily pretreated with other therapies that may cause secondary malignancies, malignant diseases were reported in patients treated with ^{131}I-omburtamab, including myelodysplastic syndrome, acute myeloid leukemia and papillary thyroid cancer.

Study 03-133

The most common adverse reactions and laboratory abnormalities are listed in Table 17.

Serious adverse reactions occurred in 50% of patients who received^{131}I-omburtamab. Serious adverse reactions that occurred in $\geq$ 5% of patients included decreased platelet count (21%), decreased neutrophil count (14%), decreased white blood cell count (10%) and decreased hemoglobin (5%).

Among the 94 patients treated ^{131}I-omburtamab, 48% were treated with one dose. Permanent discontinuation of ^{131}I-omburtamab due to an adverse event occurred in 19% of patients. Adverse events which resulted in permanent discontinuation of ^{131}I-omburtamab were decreased platelet count, decreased neutrophil count, device-related infection, seizure, headache and chemical meningitis.

Table 17: Select Adverse Reactions and Laboratory Abnormalities ≥20% in Patients with Neuroblastoma Who Received ^{131}I-omburtamab in Study 03-133

Adverse Reaction/ Laboratory Abnormality	^{131}I-omburtamab (N=94)	
	All Grades[#] (%)	Grade 3 or 4[#] (%)
Hematology		
Decreased platelets	80	49
Decreased leukocytes	78	43
Decreased neutrophils	72	41
Decreased lymphocytes	62	42
Chemistry		
Increased aspartate aminotransferase	49	4
Increased glucose	48[*]	0
Increased alanine aminotransferase	40	8
Decreased phosphorous	31	8
Decreased albumin	21	0
Gastrointestinal disorders		
Vomiting	32	3
Respiratory		
Cough	26	0
Nervous system disorders		
Headache	21	1

#patients who did not have a baseline lab value are not included in this analysis

*Does not include 3 events that do not have numerical value (e.g. change from normal glucose to hyperglycemia).

Study 101

The most common adverse reactions and laboratory abnormalities are listed in Table 18.

Serious adverse reactions occurred in 41% of patients who received ^{131}I-omburtamab. Serious adverse reactions in ≥ 5% of patients included decreased platelet count (16%), intracranial hemorrhage (9%), and decreased lymphocyte count (6%). Fatal adverse reactions occurred in 1 patient who received ^{131}I-omburtamab (case of intracranial hemorrhage).

Among 32 patients who received ^{131}I-omburtamab, 38% received one dose. Permanent discontinuation of ^{131}I-omburtamab due to an adverse event occurred in 28% of patients. Adverse events which resulted

in permanent discontinuation of ^{131}I-omburtamab in > 3% of patients were primarily related to myelosuppression with the exception of 1 case of chemical meningitis.

Table 18: Select Adverse Reactions and Laboratory Abnormalities ≥20% in Patients with Neuroblastoma Who Received ^{131}I-omburtamab in Study 101

Adverse Reaction/ Laboratory Abnormality	^{131}I-omburtamab (N=32)	
	All Grades (%)[#]	Grade 3 or 4 (%)[#]
Hematology		
Decreased platelets	94	44
Decreased leukocytes	78	50
Decreased lymphocytes	79	54
Decreased neutrophils	74	48
Decreased hemoglobin	56	9
Chemistry		
Increased alanine aminotransferase	53	6
Increased aspartate aminotransferase	47	0
Decreased bicarbonate	37	0
Decreased albumin	28	0
Decreased potassium	25	3
Decreased fasting glucose	20	0
Gastrointestinal Disorders		
Nausea	34	0
Vomiting	25	0
Nervous System Disorders		
Headache	25	0

3.2.3 Safety Issues in Detail

Key safety issue 1: Risks from off-target radiation exposure

See discussion under Section 3.2.2

Key safety issue 2: Risk from delivery of ^{131}I-omburtamab including Ommaya placement

See discussion under Section 3.2.2

Although each of these risks may be acceptable in the context of a life-threatening disease, they are not acceptable in the context of a treatment for which clinical benefit has not been established.

3.3 Risk Mitigation

If efficacy is established and there is a clear potential for clinical benefit for patients with neuroblastoma with CNS/LM metastases, the safety issues addressed above can be characterized and managed by appropriate product labeling.

4 SUMMARY

To receive FDA approval, a drug or biologic product must demonstrate substantial evidence of effectiveness through adequate and well-controlled studies (21 CFR 314.126). To establish effectiveness, it is essential to distinguish the effect of the drug "from influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation" (21 CFR 314.126[a]).

Efficacy results submitted by the Applicant rely on an assessment of Overall Survival (OS) in a single-arm trial (Study 03-133). As discussed in the FDA guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018), OS should generally be evaluated in randomized trials because data from externally controlled trials may not be reliable or interpretable. Apparent differences in outcome between external controls and current treatment groups can arise from factors other than the drug under investigation, such as differences in patient or disease characteristics, supportive care, concomitant treatments, or other factors. Randomized studies minimize the effect of both known and unknown differences between populations by providing a direct outcome comparison. If an external control is used to construct an adequate and well-controlled investigation, the external control population must be similar to the trial population regarding known factors (e.g. baseline characteristics, concomitant therapies) that can affect the primary endpoint and that could result in substantial differences in outcome unrelated to the treatment of interest.

The FDA review team identified the following three key review issues with this application:

1. The external control population is not fit-for-purpose as a comparator due to substantive differences between the study and control populations that limit the ability to attribute survival differences to the effect of ^{131}I-omburtamab.
2. Recognizing the level of evidence provided and need for regulatory flexibility, FDA performed additional analyses to examine bias and results reinforce that differences in survival cannot be reliably attributed to ^{131}I-omburtamab.
3. The application does not include reliable response rate data to provide supportive evidence of the treatment effect of ^{131}I-omburtamab.

These review issues result in a large degree of uncertainty regarding whether the observed differences in overall survival between the Study 03-133 and external control populations are due to ^{131}I-omburtamab or whether they are due to differences in other anticancer treatment, supportive care regimens, unknown differences between the two populations, or a combination of these factors.

Given the magnitude of these uncertainties and limitations, FDA requests discussion regarding the assessment of efficacy in this application.

- Discuss if real-world data (RWD) from the Central Childhood German Cancer Registry are appropriate for comparison of overall survival with Study 03-133, taking into account the known differences in the study populations and other potential sources of bias.
- Discuss whether additional information is needed to assess the benefit of ^{131}I-omburtamab for neuroblastoma with CNS/LM relapse.

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6 APPENDIX

Appendix Table: Summary of imaging assessment of responders per BICR in Study 101 and corresponding review issues.

Reported Response	BIRC Reviewer	Scan				Factors Limiting Assessment
		Baseline	5 weeks	10 weeks	26 weeks	
Confirmed Responses						
1	1	LM	SD	SD	SD	CSF cytology negative Received TMZ between 10 and 26 week scans
	2*	LM	SD	CR	CR	
2	1	LM + parenchymal	PR	PR	PR	CSF cytology negative 30-day washout period from radiation therapy to baseline MRI
	2*	LM	CR	CR	CR	
3	1*	LM + parenchymal	SD	PR	CR	19-day washout period from chemotherapy and 29-day washout from radiation therapy to baseline MRI ^{131}I-omburtamab given 60 days after baseline MRI^ Received TMZ, IRN, and DTX between first response and "confirmation" scan
	2	NED	NED	PD	PD	
4	1*	Parenchymal	SD	CR	CR	No target lesions at baseline Received naxitamab + GM-CSF between first response and "confirmation" scan
	2	NED	NED	NED	NED	
Unconfirmed Responses						
5	1*	parenchymal	PR	PD	PD	
	2	LM + parenchymal	SD	PR	PD	
6	1*	LM + parenchymal	PR	PD	PD	
	2	NED	NED	NED	NED	
7	1*	LM + parenchymal	SD	SD	CR	
	2	NED	NED	NED	NED	

*denotes adjudicated response selected by reviewer 3

For LM disease, according to EANO–ESMO response assessment guidelines, an imaging response is assessed as improved, stable or worsening. A CR represents improved imaging.

^ Per protocol, pre-treatment evaluations should be completed within 30 days of start of treatment

DTX= dinutuximab, IRN=irinotecan, LM=leptomeningeal, NED=no evidence of disease, CR=complete response, PR=partial response, SD=stable disease, PD= progressive disease BICR: blinded independent central review, TMZ: temozolomide